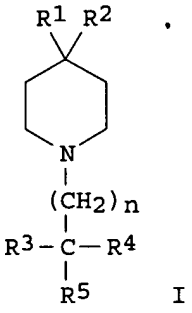
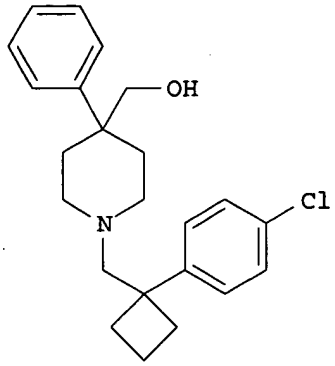
8/17/05

L6 ANSWER 14 OF 149 CAPLUS COPYRIGHT 2005 ACS on STN
GI



I



II

Applicants own

AB One aspect of the invention relates to the title compds. I [wherein R = H, alkyl, aralkyl, cycloalkyl, alkenyl, aryl, heteroaryl, acyl, or sulfonyl; R1 = aryl, or heteroaryl; R2 = RO-alkyl, (R)2N-alkyl, RS-alkyl, RO-cycloalkyl, (R)2N-cycloalkyl, or RS-cycloalkyl; R3 = H, alkyl, cycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, OR, or F; R4 = H, alkyl, cycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, OR, or F; R5 = an aryl or heteroaryl group; R3 and R4 may be connected through a covalent bond; n = 0, 1, or 2; any stereocenter can be (R), (S), or a mixture]. A second aspect of the invention relates to the use of I as ligands for various mammalian cellular receptors, including dopamine transporters. More broadly, I are (to varying degrees) ligands of dopamine, serotonin, and norepinephrine receptors and transporters. Thereby, I will find use in the treatment of, among others, addiction, anxiety, depression, sexual dysfunction, hypertension , migraine, Alzheimer's disease, obesity, emesis, psychosis, analgesia, schizophrenia, Parkinson's disease, restless leg syndrome, sleeping disorders, attention deficit hyperactivity disorder, irritable bowel syndrome, premature ejaculation, menstrual dysphoria syndrome, urinary incontinence, inflammatory pain, neuropathic pain, Lesche-Nyhane disease, Wilson's disease, and Tourette's syndrome. An addnl. aspect of the invention (no claims or data) relates to the synthesis of combinatorial libraries of I, and the screening of those libraries for biol. activity, e.g., in assays based on dopamine transporters. Examples include approx. 14 compds. I, synthetic details for most of these, some biol. activity data for all exemplified I, and syntheses of various intermediates. For instance, 4-phenylpiperidine-4-carboxylic acid (tosylate salt) underwent a sequence of: (1) N-protection with Cbz, (2) borane reduction of the acid to an alc., (3) protection of the alc. as a TBDMS ether, (4) removal of Cbz from nitrogen, (5) N-acylation with 1-(4-chlorophenyl)cyclobutanecarboxylic acid using PyBOP, NMM, and DMAP, (6) reduction of the amide to an amine using LiAlH4 in THF, and (7) desilylation, to give title compound II. The latter compound bound to norepinephrine transporter (NET) and dopamine transporter (DAT) with IC50 values of <0.1 μM, and at 5-HT transporter (5-HTT) with IC50 of <1 μM.

AN 2002:449648 CAPLUS
DN 137:33220

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TI New 4,4-disubstituted piperidines, particularly 4-aryl-1-(arylalkyl)piperidine-4-methanols and derivatives, and methods of use thereof as ligands of dopamine, serotonin, and norepinephrine receptors and transporters

IN Hoemann, Michael Z.

PA Sepracor, Inc., USA

SO PCT Int. Appl., 88 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002046156	A2	20020613	WO 2001-US47036	20011204
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
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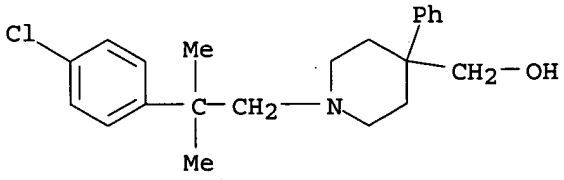
	AU 2002030665	A5	20020618	AU 2002-30665	20011204
	US 2002177607	A1	20021128	US 2001-12182	20011204
	US 6656953	B2	20031202		
	US 2004142974	A1	20040722	US 2003-722114	20031125
PRAI	US 2000-251651P	P	20001206		
	US 2001-12182	A1	20011204		
	WO 2001-US47036	W	20011204		

OS MARPAT 137:33220

IT **436162-16-2P**, [1-[2-(4-Chlorophenyl)-2-methylpropyl]-4-phenylpiperidin-4-yl]methanol
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of 4-aryl-1-(arylalkyl)piperidine-4-methanols and derivs. as ligands of dopamine, serotonin, and norepinephrine receptors and transporters)

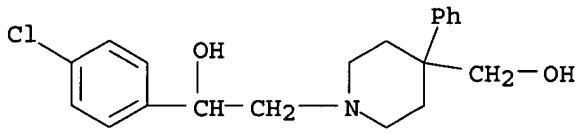
RN 436162-16-2 CAPLUS

CN 4-Piperidinemethanol, 1-[2-(4-chlorophenyl)-2-methylpropyl]-4-phenyl- (9CI) (CA INDEX NAME)

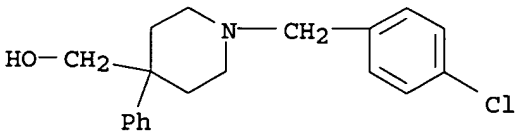


IT **436162-17-3P**, 1-(4-Chlorophenyl)-2-(4-hydroxymethyl-4-phenylpiperidin-1-yl)ethanol
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(drug candidate; preparation of 4-aryl-1-(arylalkyl)piperidine-4-methanols and derivs. as ligands of dopamine, serotonin, and norepinephrine

receptors and transporters)
RN 436162-17-3 CAPLUS
CN 1-Piperidineethanol, α-(4-chlorophenyl)-4-(hydroxymethyl)-4-phenyl- (9CI) (CA INDEX NAME)



IT **436162-06-0P**, [1-(4-Chlorobenzyl)-4-phenylpiperidin-4-yl]methanol
436162-08-2P, [1-(3-Methoxybenzyl)-4-phenylpiperidin-4-yl]methanol
436162-18-4P, Acetic acid [1-[2-acetoxy-2-(4-chlorophenyl)ethyl]-4-phenylpiperidin-4-yl]methyl ester
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of 4-aryl-1-(arylalkyl)piperidine-4-methanols and derivs. as ligands of dopamine, serotonin, and norepinephrine receptors and transporters)
RN 436162-06-0 CAPLUS
CN 4-Piperidinemethanol, 1-[(4-chlorophenyl)methyl]-4-phenyl- (9CI) (CA INDEX NAME)



RN 436162-08-2 CAPLUS
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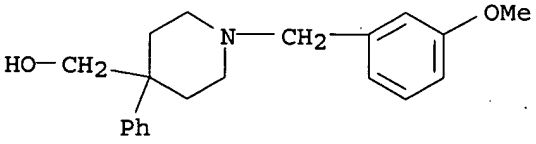
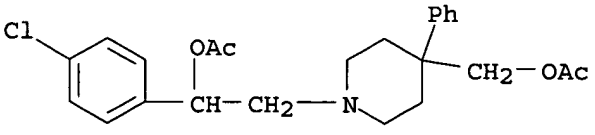


RN 436162-18-4 CAPLUS
CN 1-Piperidineethanol, 4-[(acetyloxy)methyl]-α-(4-chlorophenyl)-4-phenyl-, acetate (ester) (9CI) (CA INDEX NAME)



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IT **436162-23-1**

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